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Amitraz

Proposed Interim Registration Review Decision
Case Number 0234

June 2021

Approved by: _____

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I. INTRODUCTION

This document is the Environmental Protection Agency's (EPA or the Agency) Proposed Interim Registration Review Decision (PID) for amitraz (PC Code 106201; case 0234). In a registration review decision under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the Agency determines whether a pesticide continues to meet FIFRA's registration standard.[1] Where appropriate, the Agency may issue an interim registration review decision before completing a registration review.[2] Among other things, the interim registration review decision may determine that new risk mitigation measures are necessary, lay out interim risk mitigation measures, identify data or information required to complete the review, and include schedules for submitting the required data, conducting the new risk assessment and completing the registration review.[3] For more information on amitraz, see EPA's public docket (EPA-HQ-OPP-2009-1015) at www.regulations.gov.

FIFRA[4] mandates the continuous review of existing pesticides. All pesticides distributed or sold in the United States must be registered by EPA based on scientific data showing that they will not cause unreasonable risks to human health or to the environment when used as directed on product labeling. In 2006, the Agency began implementing the registration review program. EPA will review each registered pesticide every 15 years. Through the registration review program, the Agency intends to verify that all registered pesticides continue to meet the registration standard as the ability to assess and reduce risk evolves and as policies and practices change. By periodically re-evaluating pesticides as science, public policy, and pesticide-use practices change, the Agency ensures that the public can continue to use products in the marketplace that do not present unreasonable adverse effects. For more information on the registration review program, see http://www.epa.gov/pesticide-reevaluation.

The Agency is issuing a PID for amitraz so that it can move forward with aspects of the registration review that are complete. EPA is currently working with the U.S. Fish and Wildlife Service and the National Marine Fisheries Service (the Services) to improve the consultation process for federally listed threatened and endangered (listed) species and their designated critical habitat for pesticides under the Endangered Species Act (ESA).[5] The Agency has determined that the current registrations of amitraz present limited exposure potential to non-target organisms outside of beehives, including federally listed species. Therefore, a "No Effect" determination has been made for all federally listed species. However, pursuant to the Federal Food, Drug, and Cosmetic Act (FFDCA)[6], the Agency will complete endocrine screening for amitraz, before completing registration review. For more information on the listed-species determination and the endocrine screening for amitraz registration review see Appendices A and B.

Amitraz is an insecticide/acaricide currently registered for use in pet collars for control of ticks on dogs and as impregnated strips for control of Varroa mites in beehives. Amitraz is a member

[1] Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) § 3(g), 7 U.S.C. § 136a(g); 40 C.F.R. § 155.57.
[2] 40 C.F.R. §§ 155.56, 155.58.
[3] 40 C.F.R. § 155.56.
[4] As amended by the Food Quality Protection Act (FQPA) of 1996, Pub. L. No. 104-170, 110 Stat. 1489.
[5] Endangered Species Act (ESA) § 7, 16 U.S.C. § 1536.
[6] Federal Food, Drug, and Cosmetic Act (FFDCA) § 408(p), 21 U.S.C. § 346a(p).

of the formamidine class of insecticides. There are two currently registered products with amitraz as the active ingredient (a.i.): Preventic Tick Collar for Dogs (EPA Reg. #2382-104) and Apivar (EPA Reg. #87243-1). Amitraz was registered for use as a pet spot-on product (Certifect for Dogs, EPA Reg. No. 65331-7); however, the registrant voluntarily cancelled the product and a Federal Register notice (FRN) was issued on May 13, 2019 (84 FR 20882) announcing the final cancellation. As a result, this use has not been included in the draft risk assessments (DRAs).

This document is organized in five sections: the *Introduction*, which includes this summary and a summary of public comments and EPA's responses; *Use and Usage*, which describes how and why amitraz is used and summarizes data on its use; *Scientific Assessments*, which summarizes EPA's risk and benefits assessments, updates or revisions to previous risk assessments, and provides broader context with a discussion of risk characterization; the *Proposed Interim Registration Review Decision*, which describes any mitigation measures proposed to address risks of concern and the regulatory rationale; and, lastly, the *Next Steps and Timeline* for completion of this registration review.

A. Summary of Amitraz Registration Review

Pursuant to 40 CFR § 155.50, EPA formally initiated registration review for amitraz with the opening of the registration review docket for the case. The following summary highlights the docket opening and other significant milestones that have occurred thus far during the registration review of amitraz.

- March 2010 – The *Amitraz Preliminary Work Plan (PWP)*, the *Amitraz Human Health Assessment Scoping Document in Support of Registration Review*, and the *Problem Formulation for the Environmental Fate and Ecological Risk, Endangered Species, and Drinking Water Assessments in Support of the Registration Review of Amitraz* were posted to the docket for a 60-day public comment period.

- September 2010 – The *Amitraz Final Work Plan* (FWP) was issued. There was one public comment from Physicians Committee for Responsible Medicine (PCRM) received on the PWP. PCRM comments submitted regarding a series of animal studies which were identified as data requirements in the Summary and Scoping documents. PCRM indicated that data may already exist either with the technical registrants or other sources that could fulfill some of the Agency's data requirements, which would reduce animal testing and costs. The comments did not change the schedule, risk assessment needs, or anticipated data requirements for registration review.

- November 2011 – A Generic Data Call-In (GDCI-106201-1053) for amitraz was issued for data needed to conduct the registration review risk assessments. All data have been submitted and the GDCI has been satisfied.

- November 2018 –The Agency published the *Amitraz: Draft Human Health Risk Assessment for Registration Review in Support of Registration Review* and the *Amitraz:*

Preliminary Ecological Risk Assessment and Endangered Species Assessment for Registration Review of the Conventional Use in Honey Bee Hives for a 60-day public comment period. Seven comments were received during the comment period. These comments and the Agency's responses are summarized below.

- June 2021 – The Agency is now publishing the Proposed Interim Registration Review Decision (PID) for amitraz in the docket for a 60-day public comment period. Along with the amitraz PID, the following documents are also posted to the amitraz registration review docket (EPA-HQ-OPP-2009-1015):
    - *Amitraz: Revised Draft Human Health Risk Assessment for Registration Review* dated May 4, 2021.
    - *Amitraz: Revised Occupational and Residential Exposure Assessment for Registration Review* dated May 4, 2021.
    - *Amitraz: Data Evaluation Record for the Study "Torsion Study and Collar Placement Stimulations for the Preventic Tick Collar for Dogs (EPA Registration Number 2382-104)"* dated May 4, 2021.
    - *Amitraz: Response to Comments on the Draft Human Health Risk Assessment for Registration Review* dated July 25, 2019.
    - *Amitraz: Response to Public Comments on the Draft Ecological Risk Assessment* dated July 16, 2019.
    - *Amitraz: Transmittal of Updated Incident Data* from the Ecological Fate and Effects Division, dated June 3, 2021.

B. Summary of Public Comments on the Draft Risk Assessments and Agency Responses

During the 60-day public comment period for the amitraz draft risk assessments which opened on November 30, 2018 and closed on March 15, 2019, the Agency received public comments from seven sources. Comments were received from the United States Department of Agriculture (USDA), Bay Area Clean Area Water Agencies (BACWA), the National Association of Clean Water Agencies (NACWA), San Francisco Bay Regional Water Quality Control Board (SFBRWQCB), Veto-pharma, Virbac-AH, Inc., and Amitraz Registration Review Consortium (AARC), which is comprised of registrant companies Veto-pharma S.A. and Virbac AH Inc. The Agency's responses to substantive comments are summarized below. The Agency thanks all commenters for their comments and has considered them in developing this PID.

Comments on the Ecological Risk Assessment

Comments submitted by USDA (Docket ID EPA-HQ-OPP-2009-1015-0021)

Comment: USDA complimented EPA on the use of a streamlined approach to ecological risk assessment and offered to work with EPA regarding questions in providing information for risk assessments and benefits characterization.

EPA Response: EPA thanks USDA for their comment and looks forward to any collaboration appropriate for this case.

Comments Submitted by BACWA, NACWA, and SFBRWQCB (Docket IDs: EPA-HQ-OPP-2009-1015-0019, -0020, and -0018, respectively)

Comment: BACWA, NACWA, and SFBRWQCB expressed concerns about the potential for aquatic exposures when the water used to wash amitraz-treated dogs is released down the drain and into the sewer system, (i.e., "down-the-drain" exposures). These stakeholders asked the Agency to include an analysis in a revised ecological risk assessment that evaluates sewer discharges of amitraz from the Preventic collar. BACWA noted several studies indicating that pet flea and tick control products have a direct pathway, via sewer collection systems, to Publicly Owned Treatment Works (POTWs). All three commenters requested that the Agency determine the minimum amitraz application rate necessary for tick control to minimize quantities discharged down the drain, and to add label instructions to not wash pets with the collar on.

EPA Response: EPA appreciates BACWA, NACWA, and SFBRWQCB's comments on down-the-drain exposure scenarios. With regard to incorporating down-the-drain exposures into the ecological risk assessment, down-the-drain exposure scenarios have been explored quantitatively and qualitatively for other chemicals. However, in the recent pyrethroid and pyrethrins risk assessment (USEPA, 2016) which assessed pyrethroid releases to publicly owned treatment works (POTWs), the concentrations derived from the down-the-drain model (USEPA 2007) were demonstrated to be highly uncertain. The down-the-drain model requires multiple assumptions for input parameters that are difficult to derive or are system-specific and assumes no degradation and no sorption of the chemical to organic matter or to the sediments in the body of water. In lieu of this modeling, EPA often considers measured (*i.e.*, monitored) concentrations in influent and effluent for pesticides where down-the-drain exposures may occur. For amitraz, there are no water monitoring data available in the Water Quality Portal Database of the National Water Quality Monitoring Council (https://www.waterqualitydata.us/portal/).

Amitraz' environmental fate properties indicate that it is not a persistent compound in water and, therefore, amitraz residues are not expected to be found after the water treatment process. Additionally, the Preventic (EPA Reg. #2382-104) label already states, "…it is suggested that the collar be removed before bathing" for efficacy reasons. Although the Agency has concluded that down-the-drain exposures are not a concern for amitraz, this existing label language further reduces any potential for down-the-drain exposures. For more details, please see the *Amitraz: Response to Public Comments on the Draft Ecological Risk Assessment* (dated July 16, 2019).

Comments Submitted by Veto-pharma (Docket ID: EPA-HQ-OPP-2009-1015-0022)

Comment: Veto-pharma expressed their concerns regarding the Agency's conclusion that amitraz may result in effects to honey bees when the two most recent and most relevant incidents reported also found the presence of "other highly toxic insecticides." Veto-pharma stated it is unfair to prematurely conclude that amitraz could negatively affect honey bee health, and asserted that the available data indicated otherwise. Veto-pharma requested to continue a dialogue with the Agency on issues concerning honey bee incidents reported that involve the Apivar product.

EPA Response: The Agency understands Veto-pharma's concern and established in the draft ecological risk assessment that previously registered formulations of amitraz (*i.e.*, not Apivar) are linked to many reported incidents to honey bee colonies (see Section III.B.2. of this document). These form the basis of the concern that amitraz may have a negative effect on the honey bee colony. EPA acknowledges that other highly toxic compounds were observed in the more recent incidents associated with the Apivar product. While these incidents did not result in a more elevated risk concern to honey bee colonies, they also did not provide sufficient details to isolate the incidents to the other chemicals detected in the hives. For more details, please see the *Amitraz: Response to Comments on the Draft Ecological Risk Assessment for Registration Review* (dated July 16, 2019).

Comments on the Human Health Risk Assessment

Comments Submitted by Veto-pharma, (Docket ID: EPA-HQ-OPP-2009-1015-0022)

Comment: Veto-pharma disagrees with the Agency 's recommendation to lower the current tolerance in honey from 0.2 ppm to 0.1 ppm to harmonize with established Canadian MRLs. Veto-pharma states that decreasing the current 0.2 ppm amitraz tolerance in honey would create its own disharmony with established MRLs in the EU, and that the decrease is not necessary because there is no dietary risk concern resulting from the current 0.2 ppm tolerance established in honey.

EPA Response: The Agency has revised its recommendation and intends to maintain the current tolerance level of 0.2 ppm amitraz in honey to harmonize with the EU MRL of 0.2 ppm Although this tolerance level is higher than the Canada MRL of 0.1 ppm, and Canada is a major honey trade partner with the U.S., it is unlikely that amitraz will be found in U.S. honey above the 0.1 ppm MRL based on available data. For more details, please see the *Amitraz Response to Comments on the Draft Human Health Risk Assessment for Registration Review* (dated July 25, 2019).

Comments Submitted by Virbac-AH, Inc. and ARRC (Docket ID: EPA-HQ-OPP-2009-1015-0023 and -0024)

Comment: Virbac and the Amitraz Registration Review Consortium (ARRC) provided several comments on the Agency's human health risk assessment. With regard to amitraz exposure from the dog collar use, Virbac stated that it could confirm that amitraz is mainly released from the collar as a liquid and proposed using a time-weighted average residue transfer value. With regard to the toxicological effects of amitraz, Virbac and ARRC asserted that analysis of additional brain morphometric measurements from the low and mid dose groups of male rats found no biologically significant change in brains, that the extended one-generation reproductive toxicity study (EOGRTS) contained sufficient data to conclude that there were no effects on neurological development in young rats, and that a 10X FQPA Safety Factor is unnecessary given the comprehensive nature of the EOGRTS and other studies. Virbac and ARRC also stated that the dermal absorption factor (DAF) used in the study should be substantially reduced based on available data.

EPA Response: Since the submission of Virbac and ARRC's comments in 2019, Virbac conducted and submitted a dust torsion study that allowed further refinements to the human health risk assessment that address Virbac's concerns related to the liquid/dust question. With regard to the time-weighted average residue transfer value, EPA agreed with Virbac's proposal and incorporated it into the revised human health risk assessment.

Regarding comments on the toxicology of amitraz, EPA disagreed with ARRC on the comprehensive nature of the EOGRTS such that the 10X FQPA Safety Factor could be reduced. EPA concluded that there is still concern for lifestage sensitivity in PND 5 pups due to the lack of adequate thyroid hormone data, the most sensitive endpoint in the EOGRTS study. However, the additional brain morphometric data submitted from the EOGRTS allowed the Agency to refine the human health risk assessment and reduce the interspecies uncertainty factor to 3X. With regard to reduction of the DAF, the Agency reviewed the available data and determined that use of human *in vitro* dermal absorption data alone was appropriate. Use of these data resulted in a revised DAF of 1%, which was used in the revised human health risk assessment. These changes resulted in no risks of concern in the revised human health risk assessment.

Please see *Amitraz: Revised Draft Human Health Risk Assessment for Registration Review, Amitraz: Response to Comments on the Draft Human Health Risk Assessment for Registration Review,* and *Amitraz: Data Evaluation Record for the Study "Torsion Study and Collar Placement Stimulations for the Preventic Tick Collar for Dogs (EPA Registration Number: 2382-104)* in the public docket for additional technical clarifications and full responses to comments.

II. USE AND USAGE

Amitraz is a contact acaricide classified by the Insecticide Resistance Action Committee (IRAC) as a Group 19 (an octopamine receptor agonist) chemical, which activates receptors in the central nervous system leading to hyperexcitation in ticks and mites (IRAC 2021). The distinct biochemical mechanism of amitraz is different than from any of the other major classes of insecticides (Ahmed and Matsumura 2012). There are currently only two end-use amitraz products, one for impregnated strips for beehives and the other for impregnated dog collars. When dogs wear the collar impregnated with amitraz, they are protected from ticks for up to 90 days. In addition, upon exposure to amitraz, ticks already feeding on dogs detach and die (Hollingworth 1976, Dawkins and Gladney 1978). The strips to control varroa mites on honey bees in beehives exert control for up to 56 days.

Impregnated Strips for Beehives Usage

The only survey of beehive chemical use known to EPA is a state-level survey for use in California for the years between 2013 and 2017. The survey indicates an annual average of 300 lbs of amitraz was reported for use in beehives (CDPR, 2018).

Dog Collar Usage

According to non-agricultural market research data, 30% of respondents who owned dogs in a 2019 survey used a type of impregnated collar on dogs to target ticks (this includes all active ingredients with dog collar uses for ticks). Approximately 3,600 lbs of amitraz were reported to be used in dog collars in 2019 (NMRD, 2019b).

III. SCIENTIFIC ASSESSMENTS

A. Human Health Risks

The Agency has summarized the amitraz human health risk assessment below. The Agency used the most current science policies and risk assessment methodologies to prepare this risk assessment in support of the registration review of amitraz. For additional details on the human health assessments for amitraz, see *Amitraz: Human Health Draft Risk Assessment for Registration Review, Amitraz: Response to Comments on the Draft Human Health Risk Assessment for Registration Review,* and *Amitraz: Revised Draft Human Health Risk Assessment for Registration Review,* in EPA's public docket (EPA-HQ-OPP-2009-1015).

1. Risk Summary

The 2018 *Amitraz: Human Health Draft Risk Assessment for Registration Review* identified potential human health risks of concern for the dog collar use, including residential handler risks, residential post-application risks, and occupational handler risks.

Since the 2018 risk assessment, a revised human health risk assessment has been completed in 2021. Numerous refinements were incorporated into this assessment based on comments received and additional data submissions. As a result of these refinements, *Amitraz: Revised Draft Human Health Risk Assessment for Registration Review* concluded that there are no human health risks of concern. Changes incorporated into the revised risk assessment included:

- The use of human *in vitro* dermal absorption data alone to derive the dermal absorption factor (DAF), resulting in a revised DAF of 1%.
- Additional brain morphometric data from the extended one-generation reproduction toxicity study (EOGRTS) were submitted, evaluated, and integrated into the revised risk assessment.
- The interspecies uncertainty factor (UF) for chronic dietary, incidental oral, dermal, and inhalation exposures was reduced from 10X to 3X to account for interspecies extrapolation [reduced based on unique toxicodynamic differences in human versus rat with respect to thyroid homeostasis].
- In the previous DRA a tolerance level of 0.1 ppm was recommended for amitraz in honey. HED is now recommending that the tolerance for honey be retained at the current 0.2 ppm level based on comments received from the registrant.
- The acute and chronic dietary assessments have been revised to reflect the current tolerance level for honey. The chronic dietary assessment has been revised to reflect an updated chronic population adjusted dose (cPAD) (based on the updated UF).

- An updated pet collar assessment was completed that incorporated submitted data that allowed refinement of the liquid to dust ratio and a refined transferable residue factor from the existing transferable residue study.
- Updated residential and occupational dermal exposures reflecting an updated DAF of 1%.
- Updated residential and occupational assessments reflecting a revised level of concern (LOC) of 300 (based on the updated UF).
- An aggregate (residential plus dietary exposure) assessment was conducted. An aggregate assessment was not performed in the previous assessment.
- Updated Tier 1 review of human health incidents.

Cumulative Risks

The Agency has not made a finding that amitraz and other pesticides have a common mechanism of toxicity to humans. In addition, amitraz does not appear to produce a toxic metabolite produced by other substances. Therefore, the EPA has not assumed that amitraz has a common mechanism of toxicity with other substances for this assessment.

2. Human Incidents and Epidemiology

EPA reviewed amitraz incidents reported to the Health Effects Division database. As of EPA's latest search on August 2, 2018, there were nine cases reported to the Main Incident Data System (IDS) from January 1, 2013 to March 1, 2018, that involved the active ingredient amitraz. Of these nine case reports, four incidents involved the single active ingredient amitraz (only). These incidents involved adults and were classified as moderate severity. Three of the cases involved contact with a dog collar and the fourth involved ingestion of "dog flea medication." Reported symptoms included headache, vomiting, malaise, ocular swelling, and respiratory distress. The other five amitraz incidents reported involved multiple active ingredients. A search was conducted in Aggregate IDS. From January 1, 2013 to March 1, 2018, there were 72 incidents reported involving amitraz. Seventy incidents were classified as minor severity and two incidents had no or unknown severity.

A query of the Center for Disease Control's National Institute for Occupational Health (CDC/NIOSH) SENSOR-Pesticides database, identified 27 cases involving amitraz from 1998 to 2014. Twenty-two cases were low in severity, four cases were moderate in severity and one case was high in severity. The high severity case was a child who accidentally ingested a spoonful of flea dip mistaken by an adult for cough medicine (details in D448216). Of the 27 amitraz cases, sixteen cases were occupational, and eleven cases were non-occupational. The occupational and non-occupational case exposure scenarios are delineated in D448216. The majority of all amitraz cases (19 cases) involved the application of amitraz-containing products (including flea dips, collars, and spot-on products) onto pets. Eighty-one percent of amitraz cases reported in SENSOR were low in severity. Ocular symptoms, primarily eye pain/irritation/inflammation, were most frequently reported among cases. Dermal symptoms including skin rashes, skin redness and pain were also commonly reported. Gastrointestinal symptoms including nausea and vomiting were reported in seven cases.

In an updated search for human incidents from January 1, 2018 to April 20, 2021, in Main IDS there was one incident reported that involved the active ingredient amitraz. This incident was classified as moderate severity and involved multiple active ingredients (Amitraz, Fipronil, and S-Methoprene). There were two amitraz incidents reported in Aggregate IDS. These incidents were classified as minor severity. From 2015 to 2017, the SENSOR-Pesticides analysis identified no incidents involving amitraz.

Based on the continued low frequency of amitraz incidents reported to both IDS and SENSOR-Pesticides, there does not appear to be a concern at this time. The Agency will continue to monitor the incident information. Additional analyses will be conducted if ongoing human incident monitoring indicates a concern.

3. Tolerances

The Agency has established tolerances for amitraz under 40 CFR §180.287 for livestock commodities. EPA anticipates revisions to several current tolerances. A summary of these proposed tolerance revision is presented in Section IV. C.

Amitraz is registered for uses that result in residues in or on food. Generally, a tolerance or tolerance exemption—and for some uses, Food and Drug Administration (FDA) regulations or food contact notifications—must cover the residues or the affected food is considered adulterated. EPA has concluded that all of the necessary tolerances, exemptions, and FDA clearances are in place to cover residues resulting from amitraz's legal use.

The Agency has established tolerances for amitraze under 40 C.F.R. §180.287 for livestock commodities. EPA anticipates revocations of several current tolerances. A summary of these proposed revocations is presented in Section IV.C.

During the risk assessment process, EPA determined that additional tolerances, exemptions from the requirement of a tolerance, or FDA clearances are not necessary to cover residues in or on food from uses of amitraz. For more information, see Section IV.C, below.

4. Human Health Data Needs

The human health database for amitraz is mostly complete. However, there is the lack of thyroid hormone measurements in post-natal day 5 (PND 5) pups for all dose groups in the EOGRTS in rats to assess potential qualitative or quantitative susceptibility. The FQPA Safety Factor of 10X is retained as a database uncertainty factor. Until such data are available, a database uncertainty factor of 10X has been retained for all exposure scenarios being assessed for amitraz except for acute scenarios for which thyroid toxicity is not pertinent.

B. Ecological Risks

The Agency has summarized the 2018 ecological risk assessment below. The Agency used the most current science policies and risk assessment methodologies to prepare a risk assessment in

support of the registration review of amitraz. For additional details on the ecological assessment for amitraz see the *Amitraz: Draft Ecological Risk Assessment for Registration Review* and *Amitraz: Response to Comments on the Draft Ecological Risk Assessment for Registration Review,* in EPA's public docket (EPA-HQ-OPP-2009-1015).

1. Risk Summary

The Agency has not identified any ecological risks of concern for amitraz with the exception of potential risk to honey bees from impregnated strips placed in beehives. The Agency concluded that there are no relevant environmental exposure pathways to consider for the dog collar use. The Agency has concluded that the current registrations of amitraz present limited exposure potential to non-target organisms outside of the hive, including federally listed species. Therefore, a "No Effect" determination is made for all federally listed species. However, since the product requires honey bees to contact the product strips, exposure to honey bees within the hive is expected and there may be risk associated with these exposures. There is no reasonable expectation for any registered use of amitraz to cause direct or indirect adverse effects to federally listed threatened and endangered species. No adverse modification of critical habitat for federally listed species is expected from the use of amitraz.

2. Ecological Incidents

A search of the Incident Data System (IDS) for amitraz was conducted in support of risk assessment for reports between the time amitraz was first registered until January 2018. EPA's review of the Incident Data System (IDS) to support the 2018 ecological risk assessment yielded 88 incidents that associate use of amitraz with bee kills. Most of the incidents reported up to 2014 involved the legal use of the now cancelled in-hive "Miticur" product (Reg.# 54382-5; an impregnated strip of amitraz). In addition, there are two recently reported incidents which involved the Apivar product (Reg.# 87243-1). Where sufficient details are available for the two recent incidents, it appears that while Apivar was used in the hives as intended by the label, the presence of other highly toxic insecticides were detected (*e.g.*, Incident ID# I029385-00001). The magnitude of effects reported in these incidents ranged from several hives to thousands of hives. The Incident Data System (IDS) was reviewed for amitraz incidents that may have occurred since the draft ecological risk assessment was completed. This search excluded incidents classified as 'unlikely' or 'unrelated' and only includes incidents with the certainty categories of 'possible' or, 'probable'. There were two incidents reported since January 1, 2018, both of which were associated with bee kills. Multiple pesticides were present; therefore, there is uncertainty that the incidents were due to amitraz exposure is they are classified as "possible".

Please see the *Amitraz: Preliminary Ecological Risk Assessment and Endangered Species Assessment for Registration Review* and *Amitraz: Transmittal of Updated Incident Data* for more information about reported ecological incidents for amitraz. EPA will continue to monitor ecological incident information as it is reported to the Agency.

3. Ecological and Environmental Fate Data Needs

The environmental fate and ecological effects database for amitraz is complete. The Agency does not anticipate any further environmental fate and ecological effects data needs for amitraz.

C. Pet Incidents

A query of Aggregate Incident Data System (IDS) domestic animal incidents from January 1, 2016 to December 31, 2020 found a total of 109 reported domestic animal incidents for the amitraz pet product, Preventic Tick Collar for Dogs (Reg. No. 002382-00104). These domestic animal incidents included two animal deaths, three major severity incidents, 56 moderate severity incidents, 47 minor severity incident and one incident that had no or unknown effects (Table 2). The available aggregate incident data for this time period do not specify whether the domestic animal affected is a dog or another species. The Agency will continue to monitor domestic animal incident data as it is reported to the Agency.

"In its efforts to protect pets under FIFRA, EPA intends to request enhanced incident reporting and sales data for pet products akin to what is already submitted for spot-on products (https://www.epa.gov/pets/epa-evaluation-pet-spot-products-analysis-and-plans-reducing-harmful-effects). These data would allow the Agency to conduct a comparative assessment of pet incidents across registered pet products based on sales data to better determine whether any changes to the pet product registrations and labels are necessary. EPA is interested in feedback from stakeholders on the most efficient way these data can be provided to the Agency and types of analyses that could be submitted to expedite the Agency's assessment. EPA is also considering additional measures that could enhance its oversight of pet products, such as additional targeted studies and monitoring, and welcomes public comments on these and other potential measures."

Table 2. Preventic Tick Collar (Reg. No. 002382-00104) Aggregate Incidents 2016-2020 (OPP Aggregate IDS)

Years	Animal Death	Major Severity	Moderate Severity	Minor Severity	No or Unknown Effects
2016	1	0	31	28	0
2017	0	2	16	10	1
2018	1	1	6	5	0
2019	0	0	3	2	0
2020	0	0	0	2	0
Grand Total	2	3	56	47	1

D. Benefits Assessment

Benefits of impregnated strips to control varroa mite in honey bee hives

The varroa mite, *Varroa destructor* (hereafter varroa), is the only target pest of amitraz-impregnated strips for use in honey bee (*Apis mellifera*) hives. Varroa is a parasite that feeds destructively on fat bodies in pupae and adult honey bees. Varroa also transmits many viruses to its host, including deformed wing and black queen cell, both of which are closely associated with significant colony losses (Sinkevich 2020). Minimizing harm to honey bees is essential while simultaneously controlling varroa. Including amitraz-impregnated strips, chemical control products labelled for control of varroa in honey bee hives are synthetic pesticides (amitraz, tau-fluvalinate, and coumaphos), two organic acids (formic and oxalic acids), and two plant derivatives (thymol and hop beta acids).

Amitraz, tau-fluvalinate, and coumaphos were used early and widely after varroa's introduction into the United States. However, there is now widespread control failure due to high levels of resistance to tau-fluvalinate and coumaphos (DeGrandi-Hoffman et al. 2012, Rinkevich 2020, Peck 2021). In addition, wax absorbs and maintains high levels of tau-fluvalinate and coumaphos (both lipophilic chemicals), and varroa are constantly exposed to sub-lethal levels of pesticide residues (Rinkevich 2020), likely contributing to pesticide resistance issues. Constant presence of tau-fluvalinate and coumaphos in the wax may also harm developing bees (DeGrandi-Hoffman et al. 2012, Peck 2021).

While organic acids and plant derivatives also provide effective control, there are limitations with each respective chemistry. Formic and oxalic acids and thymol are sensitive to ambient temperatures (DeGrandi-Hoffman et al. 2012, Peck 2021), and efficacy of thymol is also affected by humidity and colony size (DeGrandi-Hoffman et al. 2012). Higher temperatures with formic acid applications can harm bees and cause queen loss (DeGrandi-Hoffman et al. 2012). Thymol imparts a detectable odor to treatment equipment and in honey (Peck 2021). Impregnated strips with hop beta acids need to be reapplied more frequently, every 14 to 30 days, compared to amitraz-impregnated strips that last up to 56 days.

Amitraz is considered by beekeepers to be a highly effective miticide of choice (Peck 2021). However, resistance to amitraz was reported in Minnesota shortly after its initial use in the late 1990's (Elzen et al. 2000). In 2019, amitraz resistance was suspected and ultimately detected from among some of the sampled commercial apiaries in Louisiana, New York, and South Dakota. Apiaries had at least a three-year history of using amitraz, and despite a long history of amitraz use, five of the eleven apiaries had no or low levels of resistance (Rinkevich 2020). Despite significant variation in control of varroa across individual colonies in an apiary or apiaries within the larger operation, amitraz is still regarded as an effective varroa control option (Rinkevich 2020).

In conclusion, amitraz-impregnated strips are the preferred tool by apiarists for control of varroa (Peck 2021). Amitraz does not have temperature, humidity or colony size limitations when applied to beehives. With the exception of tau-fluvalinate, amitraz has the longest treatment duration of the available products. This provides a convenience to end users in limiting the number of times retreatment of colonies is needed. Overall, amitraz-impregnated strips provide end users with an application method and chemical properties that may be preferable to other available varroa control products, some of which have widespread resistance issues.

Benefits of impregnated dog collars to control ticks

Multiple species of ticks are targets of amitraz in impregnated dog collars. Amitraz is part of a suite of active ingredients that help to control tick species of public health concern, including the brown dog tick (*Rhipicephalus sanguineus*), American dog tick (*Dermacentor variabilis*), and blacklegged tick (*Ixodes scapularis*) on domestic dogs. Tick prevention not only protects dogs, it also prevents the transport of ticks into the home. For dogs in the U.S. in 2020, there were almost 900,000 cases of tick-borne disease reported (CAPC, 2021). Some ticks carry pathogens that can lead to sixteen different human diseases (CDC, 2020). The blacklegged tick, for example, vectors the pathogen that causes Lyme disease in humans. Between 2017 and 2019, there was a national mean cumulative incidence of 49 Emergency Department (ED) tick bite visits per 100,000 ED visits overall, with the highest incidence of 110 tick bite visits per 100,000 visits to the ED in the Northeastern U.S. alone (Marx et al. 2021).

For controlling ticks on dogs, pet owners have multiple options, among which include the use of a collar impregnated with insecticide, spot-on treatments containing insecticides, or a prescribed veterinary medication. These three types of products were the most used among respondents in 2019 for controlling ticks on dogs (NMRD 2019a). All commercially available collars can be applied to dogs to provide three to eight months of protection against ticks. This is in contrast to spot-on treatments and some veterinary medicine (prescription only) chewable tablets that provide a single month of control against the same pests. The Agency's earlier review of pet products that are possible alternatives to the pet collars impregnated with the organophosphate tetrachlorvinphos concluded that pet spot-ons are less convenient because they must be reapplied every month (Atwood and Smearman 2017). Veterinary medicines require a prescription, with pet owners incurring the additional cost of an office visit, thus they tend to be less convenient to obtain and use (Atwood and Smearman 2017). Amitraz-impregnated collars may be more convenient than many likely alternative products, including more commonly used pet spot-ons and veterinary medicines, because the amitraz collar is applied for three months of control, and a prescription from a veterinarian is not required to obtain it.

Collars containing insecticides other than amitraz are equally as convenient as those with amitraz and may cost less monthly than amitraz collars (Atwood and Smearman 2017). However, acaracide resistance is a concern with any tick species of public health importance. There is documented resistance to permethrin and tolerance to fipronil among populations of the brown dog tick in Florida and Texas (Eiden et al. 2015). These two active ingredients are found in many pet products. For areas where there is acaricide resistance, amitraz may provide another control option for ticks on dogs.

In conclusion, amitraz-impregnated dog collars may be more convenient and/or cost-effective than many likely alternative products. Amitraz is important in tick control since it provides an additional mode of action when resistance occurs with other active ingredients.

IV. PROPOSED INTERIM REGISTRATION REVIEW DECISION

A. Proposed Risk Mitigation and Regulatory Rationale

The Agency has reviewed the risks and benefits associated with the registered uses of amitraz in developing this Proposed Interim Registration Review Decision. The Agency has determined that there are no human health or ecological risks of concern except for potential risk to honey bees from impregnated strip use in beehives. EPA has also made a "no effect" determination for currently registered uses of amitraz under the Endangered Species Act for all listed species and designated critical habitat for those species.

While there are potential risks to honey bees from amitraz strip use, these risks are likely much lower than alternative chemistries that target varroa mite. Additionally, this use provides benefits to beekeepers because of amitraz's long duration of efficacy (and corresponding limited need for retreatment) as compared to many alternatives, an application method preferred by many beekeepers, and amitraz's lack of temperature, humidity or colony size limitations when applied to beehives. Based on the limited risk profile and the aforementioned benefits, the Agency is not proposing any mitigation and has concluded that the FIFRA registration standard is met for the use of amitraz-impregnated strips in beehives.

To determine whether the FIFRA registration standard is met for the dog collar use, EPA intends to request enhanced incident reporting and sales data for the Preventic collar akin to what is submitted for spot-on products (https://www.epa.gov/pets/epa-evaluation-pet-spot-products-analysis-and-plans-reducing-harmful-effects). These data would allow the Agency to conduct a comparative assessment of pet incidents across registered pet products based on sales data to better determine whether any changes to the pet product registrations and labels are necessary. EPA is interested in feedback from stakeholders on the most efficient way these data can be provided to the Agency and types of analyses that could be submitted to expedite the Agency's assessment.

B. Environmental Justice

EPA seeks to achieve environmental justice, the fair treatment and meaningful involvement of all people, regardless of race, color, national origin, or income, in the development, implementation, and enforcement of environmental laws, regulations, and policies.

Pet collars are a readily available and relatively inexpensive way of controlling pests on companion animals, providing an affordable option for lower income populations. For example, ticks are important public health pests, and amitraz-impregnated dog collars may be more convenient and/or cost-effective for their control than other products (See Benefits Assessment Section III.D) that require veterinarian visits.

To help address potential environmental justice issues related to registration review decisions, the Agency seeks information on any groups or segments of the population who, as a result of their location, cultural practices, or other factors, may have atypical, unusually high exposure to amitraz compared to the general population or who may otherwise be disproportionately affected by the use of amitraz as a pesticide.

C. Tolerance Actions

There are no Codex MRLs established for amitraz. The European Union (EU) has established an MRL for amitraz residues in honey at 0.2 ppm. Canada has established an MRL of 0.1 ppm in honey which is lower than the U.S. tolerance of 0.2 ppm. The Agency has no objection to maintaining the current 0.2 ppm level.

The Agency anticipates that tolerances for residues of amitraz in livestock commodities will be revoked as shown in Table 1 below as there are no longer registered uses on livestock (dermal treatment) and there are no uses on livestock feedstuffs. The Agency intends to undertake these tolerance actions pursuant to its Federal Food, Drug Cosmetic Act (FFDCA) authority.

The Agency anticipates the following changes to the tolerances for amitraz which are summarized in Table 1 below.

Table 1. Summary of Anticipated Tolerance Revisions for Amitraz: 40 CFR §180.287

Commodity/Correct Definition	Established Tolerance (ppm)	Anticipated Tolerance (ppm)	Comments
Cattle, fat	0.1	Revoke	No U.S. registrations on livestock or feedstuffs
Cattle, meat	0.02		
Cattle, meat byproducts	0.2		
Hog, fat	0.1		
Hog, kidney	0.1		
Hog, liver	0.1		
Hog, meat	0.05		
Hog, meat byproducts	0.3		
Milk	0.03		
Milk, fat	0.2		

ppm=parts per million; equivalent to milligrams per kilogram [mg/kg].

D. Proposed Interim Registration Review Decision

The Agency is issuing this PID in accordance with 40 CFR §§155.56 and 155.58. Except for the Endocrine Disruptor Screening Program (EDSP) the Agency has made the following proposed interim decision: 1) EPA proposes that no additional data are needed at this time except enhanced pet incident and sales data, which the Agency intends to request through a separate action; and 2) no changes to the affected registrations and their labeling are needed at this time, as described in Section IV. A of this document. Although the Agency would prefer to have thyroid hormone measurements in post-natal day 5 (PND 5) pups for all dose groups in the EOGRTS and thereby remove the 10X FQPA Safety Factor, the Agency has determined that these data are not needed at this time because no human health risks were identified with the FQPA Safety Factor of 10X.

EPA did not identify any human health or ecological risks of concern apart from potential adverse effects to honey bees from impregnated strip use in beehives. Risks to honey bees from this use are likely much lower than alternative chemistries that target varroa mites and provide cost, convenience, and flexibility benefits to beekeepers. Therefore, the Agency is not proposing any mitigation for this use and has concluded that the FIFRA registration standard is met for the use of amitraz-impregnated strips in beehives.

To determine whether the dog collar use meets the FIFRA registration standard, EPA intends to request enhanced incident reporting and sales data that will help the Agency determine whether any changes to the dog collar registration and label are necessary.

In this PID, the Agency is making no human health or environmental safety findings associated with the Endocrine Disruptor Screening Program (EDSP) screening of amitraz. The Agency's final registration review decision for amitraz will be dependent upon the result of the EDSP FFDCA § 408(p) determination. For more information, see Appendix B.

E. Data Requirements

No additional data are anticipated to be called in for registration review at this time, as EPA intends to request submission of enhanced pet incident and sales data as a separate action.

V. NEXT STEPS AND TIMELINE

A. Proposed Interim Registration Review Decision

A Federal Register Notice will announce the availability of this PID for amitraz and will allow a 60-day comment period. If there are no significant comments or additional information submitted to the docket during the comment period that leads the Agency to change its PID, EPA may issue an interim registration review decision for amitraz. However, a final decision for amitraz may be issued without the Agency having previously issued an interim decision. A final decision on the amitraz registration review case will occur after an EDSP FFDCA § 408(p) determination.

B. Implementation of Mitigation Measures

Because the Agency is not proposing mitigation measures or label language clarifications for registration review for amitraz, the Agency does not anticipate the need for amended amitraz labels.

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Appendix A: Endangered Species Act Determination

There is no reasonable expectation for any registered use of amitraz to cause direct or indirect adverse effects to threatened and endangered species. No adverse modification of critical habitat is expected from the use of amitraz. This is because of lack of exposure to listed species from currently registered amitraz uses. EPA has made a "no effect" determination under the Endangered Species Act (ESA) for all listed species and designated critical habitat for such species and has therefore concluded that consultation with the U.S. Fish and Wildlife Service and the National Marine Fisheries Service under ESA § 7(a)(2) is not required.

Appendix B: Endocrine Disruptor Screening Program

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, sub-chronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its most recent registration decision for amitraz, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA § 408(p), amitraz is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA § 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. The Agency has reviewed all the assay data received for the List 1 chemicals and the conclusions of those reviews are available in the chemical-specific public dockets. A second list of chemicals identified for EDSP screening was published on June 14, 2013,[7] and includes some pesticides scheduled for Registration Review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors. Amitraz is not on either list. For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines, and the Tier 1 screening battery, please visit EPA website.[8]

[7] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.

[8] https://www.epa.gov/endocrine-disruption

In this PID, EPA is making no human health or environmental safety findings associated with the EDSP screening of amitraz. Before completing this registration review, the Agency will make an EDSP FFDCA § 408(p) determination.